compound according to Claim 1 to treat the pathological condition, to a mammal in need of such treatment.

REMARKS

Claims 1-23 are active in the present application. The claims have been amended for clarity. No new matter is added. Favorable reconsideration and allowance of all pending claims is requested.

The rejection of Claims 1-23 under 35 U.S.C. § 112, first paragraph is respectfully traversed.

Contrary to the position that the Examiner has taken, the claimed invention is enabled by the specification for the following reasons.

On pages 22-23, the specification describes how to make the compounds consistent with the scope of the claimed compounds, which include general methods of amino acid and peptide synthesis.

On page 8, lines 1-8 the specification describes that:

> New agents which limit the pro-inflammatory actions of C5a have potential for inhibiting chronic inflammation, and its accompanying pain and tissue damage. For these reasons, molecules which prevent C5a binding to its receptors are useful for treating chronic inflammatory disorders driven by complement activation. Importantly, such compounds provide valuable new insights to mechanisms of complement-mediated immunity.

On page 11, lines 29-30, the specification describes that:

> The invention provides cyclic and non-cyclic modulators of the activity of G-coupled-protein receptors

On pages 26 and 27, the specification describes assays for testing the claimed compounds, including receptor binding assays, a myeloperoxidase release assay; and *in vivo* anti-inflammatory activity, which include carrageenan paw oedema and adjuvant arthritis.

On pages 37, 39, 41 and42 the specification also describes data relating to neutropenia and C5a antagonism where the results are depicted in Figures 8 and 9 and described on page 45.

Therefore, the specification provides several well-known, reproducible, and well-accepted assays for testing the activity of the claimed compounds.

The Examiner cites work published the *British Journal of Pharmacology*, Vol. 128, pages 1461-1466 (1999) by the inventors and other authors (Paczkowski et al, a copy is attached) as allegedly supporting the Examiner's position that the art is unpredictable (see pages 6-7 of the Official Action). However, the Examiner's reliance on this publication is misplaced.

The statement referenced by the Examiner on page 461, 2nd column Paczkowski et al relates to the knowledge available prior to the present invention and for which the present application aims to provide a solution. Paczkowski et al describe data for two small molecule antagonists, one linear and one cyclic, the cyclic compound is one compound claimed in the present application. The data in Paczkowski et al show some minor differences in the way those two small molecule C5 antagonists interact with C5a receptors in two cell types: macrophages and polymorphonuclear granulocytes (see "Discussion" on page 1465). Paczkowski et al speculate that based on unspecified and unknown differences there may be two types of C5a receptors. However Paczkowski et al provides no evidence to support this speculation and, in fact, Paczkowski et al clearly describe that only one gene for the C5a receptor has been described referencing Gerard & Gerard (Nature, 349, 614-617 (1991), a copy is enclosed) (see page 1461, 2nd column, last paragraph).

Regardless of any Paczkowski et al speculations in the publication, the compounds are demonstrated to be potent C5a receptor antagonists. Both compounds are insurmountable or non-competitive antagonists, and both bind with high affinity to the C5a receptors on

macrophages and PNMS, which suggests similar attributes *in vivo*. Absent a significant difference in the way C5a receptors interact with antagonists on different cells, it is highly predictable that C5a receptors *in vivo* can be blocked with C5 antagonists.

The specification provides well-accepted models for rheumatoid arthritis tissue graft rejection(see, for example, Example 8); and animal models for systemic lupus, erythematosus (the NZB mouse), multiple sclerosis, (experimental allergic encephalomyelitis), Alzheimer's disease are commonly used to assess the efficacy of therapeutics to treat those disorders. All of these animal models yield highly reproducible responses and therapeutic outcomes to C5 antagonists when the drug is administered by a variety of routes, such as topical, intravenous and/or oral.

In support of this position, Applicants attach several publications confirming the predictability of the animal models and further demonstrate the efficacy of the claimed compounds.

Arumugam et al, (*Journal of Surgical Research* 103, 260-267, (2002)) conclude "that a potent antagonist of C5a receptors on human cells protects the rat's small intestine from I/R injury after oral or intravenous administration. Small molecule C5a antagonists may have some therapeutical utility and reperfusion injury." (see page 260, col. 1, last paragraph, conclusion").

Strachan et al (*Journal of Immunology*, 164, 6560-6565, 2000) conclude that "these results indicate potent anti-inflammatory activities of a new C5a receptor antagonists and provide more evidence for a key early role of C5a and sepsis and the reverse arthus reaction. The result supportive role for antagonists for C5a receptors in a therapeutic intervention of immuno in inflammatory disease states such as sepsis and immune complex disease." (See the last two sentences of the Abstract).

Strachan et al (*British Journal of Pharmacology*, 134: 1778-1786 (2001)) conclude that "we have shown for the first time the pharmacological activity of a small molecule C5aR antagonists following either oral or topical administration. As such, ACF-[OPdChaWR] (or an analog) is a novel drug candidate with potentially greater usefulness in the clinical setting than other large molecule C5a-inhibiting agent currently under investigation." (see page 1785, col. 2, last paragraph).

Woodruff et al (which is expected to be published in *Arthritis and Rheumatism* shortly) conclude "inhibiting the action of C5a in this model significantly reduce joint pathology, which ibuprofen was not effective. C5 antagonist could therefore have broader therapeutic benefits as anti-arthritic agents for rheumatoid arthritis than nonsteroidal anti-inflammatory drugs." (See page 1, col. 1 "conclusion").

Therefore, not only has the specification provided a full disclosure of the invention with respect to how to make and use the invention, there is additional evidence consistent with description in the specification which enables the full scope of the present invention. Therefore, the claims are, in fact, fully enabled by the specification as originally filed. Withdrawal of this ground of rejection is requested.

The rejection of Claims 1-23 under 35 U.S.C. § 112, second paragraph is believed to have been obviated by amendment.

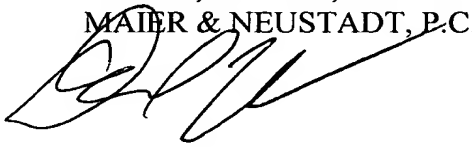
Applicants have submitted an Abstract in compliance with 37 C.F.R. § 1.72(b).

Applicants wish to thank the Examiner for withdrawing the election of species requirement and examining the full scope of the present claims.

Applicants submit that the present application is now ready for allowance. Early notification of such allowance is kindly requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Norman F. Oblon
Attorney of Record
Registration No. 24,618

Daniel J. Pereira, Ph.D.
Registration No. 45,518

22850

(703) 413-3000
Fax #: (703) 413-2220
NFO/DJP/law

I:\USER\DJPER\106480001-AM.DOC

Marked-Up Copy
Serial No: 09/446,109
Amendment Filed on: HEREWITH

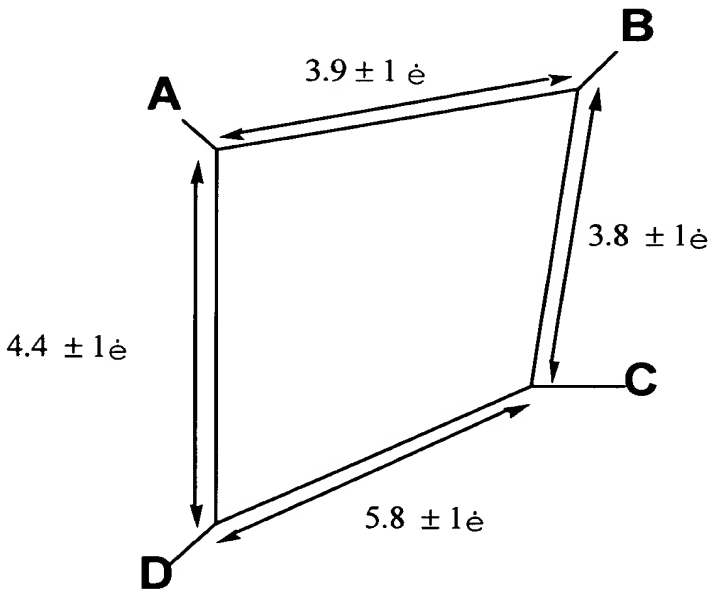
IN THE SPECIFICATION

Page 63, after the last line, beginning on a new page, please insert the attached Abstract.

IN THE CLAIMS

1. (Twice Amended) A compound which is an antagonist of a G protein-coupled receptor, which has no agonist activity, and which has a cyclic or constrained acyclic structure adapted to provide a framework of approximate dimensions as set out in Structure I:

Structure I



where the numerals refer to distances between C_α carbons of amino acids or their analogues or derivatives, and A, B, C and D are not necessarily on adjacent amino acids, or analogues or derivatives thereof; and

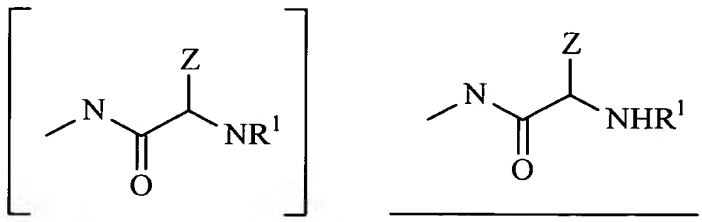
where the critical amino acid side chains are designated by A, B, C and D, where

A is any common or uncommon, basic, charged amino acid side chain which serves to position a positively charged group in this position;

B is any common or uncommon, aromatic amino acid side chain which serves to position an aromatic side-chain in this position;

C is any common or uncommon, hydrophobic amino acid side chain which serves to position any alkyl, aromatic or other group in this position;

D is any common or uncommon, aromatic amino acid which serves to position an aromatic side-chain in this position, and has the structure:



where Z is indole, indole methyl, benzyl, benzene, naphthyl, naphthyl methyl, or a derivative thereof; and

R^1 is H or an alkyl, aromatic, acyl or aromatic-acyl group.

5. (Twice Amended) An antagonist according to Claim 1, which is a constrained acyclic compound, [and comprises] comprising a type II β-turn.

8. (Twice Amended) An antagonist according to Claim 1, of formula

Ac-Phe-[Lys-Pro-(dCha)-Trp-Arg] or

Ac-Phe-[Orn-Pro-(dCha)-Trp-Arg].

[Ac-phe-[lys-pro-(dCha)-trp-arg] or
Ac-phe-[orn-pro-(dCha)-trp-arg]]

13. (Twice Amended) An antagonist according to Claim 10, selected from the group consisting of AcF-[KpdChaWR], AcF-[OPdChaWR], F-[XPdChaWR], F-[XPdChaWR], F-[X^2PdChaWR], F-[X^2PdChaWR], AcF-[OPdChaWR], AcF-[OPdChaWR], [FWPdChaWR], AcF-[KMdChaWR], AcF-[KKdChaWR], AcF-[XPdChaWR], AcF-[X^2PdChaWR], AcKF-[OPdChaWR], F-[OPdChaWR], F-[KPdChaWR], F-[OPdChaWR] and F-[KPdChaWR], wherein X is (CH_2)-NH_2 and X^2 is $(CH_2)_2$-NH_2 [compounds 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 and 28].

14. (Twice Amended) An antagonist according to Claim [13] 10, in which n is 2 or 3.

21. (Twice Amended) A method of treatment of a pathological condition mediated by a G - protein-coupled receptor, comprising the step of administering an effective amount of a compound according to Claim 1 to treat the pathological condition, to a mammal in need of such treatment.